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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/559,148	08/17/2006	Jane Louise Holley	41577/323890	9062

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EXAMINER
MAASHO, KERIMA K

ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/559,148	HOLLEY ET AL.	
	Examiner	Art Unit	
	Kerima Maasho	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *19-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12/05/2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/11/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election of group I (claims 1-18) in the reply filed on 07/18/2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical composition comprising a large and a small binding fragment of an antibody which binds Botulinum toxin, does not reasonably provide enablement for ANY toxin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicants claim and disclose a pharmaceutical composition comprising a combination of antibody fragments which bind toxin. The term "toxin" is extremely broad and could include as stated in the disclosure poisons and venoms produced by living organisms, such as bacteria, plants, snakes or insects or it may also include synthetic

poisons. However, Applicants do not provide disclosure to any other type of toxin besides Botulinum toxin. The antibody fragments disclosed with examples are to Botulinum toxin and the serotypes A-G. This rejection is based on the scope of enablement.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

"The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation."

Working example: While applicants disclose the effect of a pharmaceutical composition comprising of fab and f(ab)2 antibody fragments that bind botulinum toxin in examples 1-3 conducted in mice, all examples are in relation to Botulinum toxin. Therefore, applicants are not in possession of a composition for the treatment of any other type of toxin, venom or synthetic toxin.

State of the art: The state of the art with regard to the choice of antibody fragments to treat bacterial toxins and venoms appears to be different. Vaz et al (MIRCEN Journal,

1988, filed in IDS) teach a higher protective activity of fab' fragment compared to f(ab')2 and IgG on experimental tetanus. Ismail et al (Toxicon, 1998, filed in the IDS) teach that f(ab')2 to be the most suitable fragment to use in serotherapy of scorpion and snake envenoming when compared to fab'. Moreover, Ismail et al teach that a slower distribution of fab', when compared to f(ab')2 in rabbits and mice and IgG in rabbits rendered it inferior to both f(ab')2 and IgG. Therefore, it appears that there is a difference between venom and bacterial toxins in the use of antibody fragments. It would also appear that there would be undue experimentation to determine if combination of the fragments would be beneficial in efficiently neutralizing a given toxin other than Botulinum, and given the above teachings where f(ab')2 or fab' is more beneficial as a single fragment, to determine the ratio of the fragments that would be most effective.

Genentech Inc. v. Novo Nordisk A/S (CAFC) 42 USPQ2d 1001 clearly states: "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." This requirement has not been met in the

specification with regard to a pharmaceutical composition comprising a large and a small binding fragment of an antibody which binds to any target toxin.

Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be considered that the skilled artisan would have had to conduct undue and excessive experimentation in order to practice the claimed invention as broadly claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

2. Claims 1-4 and 6-18 are rejected under 35 U.S.C. 102(e) as being anticipated by Pomato et al (US 2005/0042775, filed May 19, 2004).

The claims of the instant invention are drawn to a pharmaceutical composition comprising (i) a first specific binding agent selected from an antibody or a large binding fragment of an antibody which specifically binds a target toxin, and (ii) a second specific

binding agent which comprises a small binding fragment of an antibody which binds said toxin, wherein first specific binding agent comprises a large binding fragment of an antibody (claim 2), wherein the large binding fragment of an antibody is an F(ab').sub.2 or F(ab).sub.2 fragment (claim 3), wherein the first specific binding agent is an antibody which is IgG or IgT (claim 4), wherein the second specific binding agent comprises an Fab, Fab', a single chain (sc) antibody or an FV, VH or VK fragment (claim 6), wherein the second specific binding agent comprises an Fab or Fab' fragment (claim 7), wherein the first and/or second binding agents are derived from polyclonal antibodies (Claim 8), wherein the first and/or second binding agents are derived from monoclonal antibodies (claim 9), wherein at least one of the first or second specific binding agents includes a section corresponding to part of the Fc region of an antibody (claim 10), wherein the toxin is a Botulinum toxin (claim 11), wherein the first and second specific binding agents bind at least one of type A, B, C, D, E, F or G botulinum toxin (claim 12), wherein the composition comprises sets of first and second specific binding agents each set of specific binding agents binding a different one of botulinum toxins A, B, C, D, E, F or G (claim 13), wherein the w/w ratio of the first specific binding agent to the second specific binding agent is in the range of from 90:10 to 10:90 (claim 14), wherein the w/w ratio of the first specific binding agent to the second specific binding agent is in the range of from 70:30 to 30:70 (claim 15), wherein the w/w ratio of the first specific binding agent to the second specific binding agent is in the range of from 60:40 to 40:60 (claim 16). The composition further comprises a pharmaceutically acceptable carrier or excipient

(claim 17). The composition is suitable for oral, parenteral, or intranasal administration, or for administration by inhalation or insufflation (claim 18).

Pomato et al teach a botulinum antitoxin composition comprising of **$F(ab)_2$** and **Fab** fragments [0014 and 0028]. The $F(ab)_2$ reads on the first specific binding agent comprising a large binding fragment of the instant invention as does the Fab on the second specific binding agent. Pomato et al teach that the antibody fragments were derived from purified **IgG** and **IgT** that have antitoxin activity and that these antibodies could be manufactured as fragmented **polyclonal** or **monoclonal** antibodies [0044]. Pomato et al teach that the antibody fragments bind the botulinum toxin, and that the antitoxin antibodies were made to Botulinum toxin serotypes **A, B, C, D, E, F, and G** [0031 and 0039]. Pomato et al further teach a composition comprising at least 60% $F(ab)_2$ and 40% Fab (**60:40**), reads on the instant claimed range for the first and second binding agent to be from 60:40 to 40:60 and is within the range of 70:30 to 30:70. Pomato et al also teach lactose as an **excipient** used in the formulation and also suggest that a variety of excipients other than lactose, such as for example sucrose, maltose or fructose can be used [0016 and 0069]. Pomato et al also teach the antitoxin fragment composition that is suitable for injection (**parenteral**) (p 8, Table 3 and [0057]). In the instant invention claim 10 refers according to any of the preceding claims, to a section in the binding agents corresponding to part of the **Fc region** of an antibody, claim 4 refers to the first specific binding agent is an IgG or IgT, as such the IgG or IgT will have the claimed part of the Fc region.

Therefore, the composition of Pomato et al anticipates claims 1-4 and 6-18 of the present invention in its entirety as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pomato et al further in view of Stockwin et al (Biochem Soc Trans, 2003, vol 31, p 433-6).

Claim 5 is drawn to a pharmaceutical composition comprising a first and second binding fragment of an antibody which binds toxin, wherein the antibody is humanized.

Pomato et al as set forth supra meets all the limitations of the instant invention, however, they do not teach the development of a humanized antibody.

Stockwin et al teach the advantages of generating humanized antibodies whereby it has a major effect on immunogenecity, effector function and half-life as well as the issue of repeated antibody dosing at high levels with limited toxicity.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to make a humanized antibody given the advantages of using humanized antibodies (for treatment in humans) which would result in fewer side

effects and improved efficacy. One of ordinary skill would have been motivated to incorporate the teachings of Stockwin et al to the teachings of Pomato et al, with reasonable expectation of success because it would have resulted in an antibody that has a lower toxicity and increased half-life with diminished immune reaction.

Conclusion

Claims 1-18 are rejected as explained above.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kerima Maasho whose telephone number is 571-270-3055. The examiner can normally be reached on Monday-Thursday, 7:30am-5:00pm, ALT. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0906. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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